
Mechanisms of telomere loss and their consequences for chromosome instability.

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Authors:	Keiko Muraki, Kristine Nyhan, Limei Han, John P Murnane
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Public Summary:

This review focuses on how the caps on the ends of chromosomes, called telomeres, protect chromosomes and keep them stable. The loss of a telomere can result in chromosome instability, which can lead to many of the alterations in DNA that result in cancer or genetic disease. Telomere loss or the loss of telomere function can occur through a variety of mechanisms. Telomere loss can occur through excessive cell division, because telomeres become slightly shorter every time a cell divides. Telomeres can also be lost suddenly, when DNA breaks near telomeres due to cell stress or damage to DNA by ionizing radiation or other toxic agents. Finally, telomeres can fail to function due to the loss of proteins that are critical to the formation of the cap structure. Telomeres are particularly sensitive to cell stress and are not repaired as efficiently as other DNA in the cell. Understanding the function of telomeres and factors that affect telomere loss is an important goal in preventing chromosome instability in human embryonic stem cells and cancer cells.

Scientific Abstract:

The ends of chromosomes in mammals, called telomeres, are composed of a 6-bp repeat sequence, TTAGGG, which is added on by the enzyme telomerase. In combination with a protein complex called shelterin, these telomeric repeat sequences form a cap that protects the ends of chromosomes. Due to insufficient telomerase expression, telomeres shorten gradually with each cell division in human somatic cells, which limits the number of times they can divide. The extensive cell division involved in cancer cell progression therefore requires that cancer cells must acquire the ability to maintain telomeres, either through expression of telomerase, or through an alternative mechanism involving recombination. It is commonly thought that the source of many chromosome rearrangements in cancer cells is a result of the extensive telomere shortening that occurs prior to the expression of telomerase. However, despite the expression of telomerase, tumor cells can continue to show chromosome instability due to telomere loss. Dysfunctional telomeres in cancer cells can result from oncogene-induced replication stress, which results in double-strand breaks (DSBs) at fragile sites, including telomeres. DSBs near telomeres are especially prone to chromosome rearrangements, because telomeric regions are deficient in DSB repair. The deficiency in DSB repair near telomeres is also an important mechanism for ionizing radiation-induced replicative senescence in normal human cells. In addition, DSBs near telomeres can result in chromosome instability in mouse embryonic stem cells, suggesting that telomere loss can contribute to heritable chromosome rearrangements. Consistent with this possibility, telomeric regions in humans are highly heterogeneous, and chromosome rearrangements near telomeres are commonly involved in human genetic disease. Understanding the mechanisms of telomere loss will therefore provide important insights into both human cancer and genetic disease.

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